CLAIMS

What is claimed is:

1. A method of making compounds of Formula I:

$$R^3$$
 R^4
 Z
 R^2
 $N-R^4$
 N
 N

wherein

5

10

15

20

R¹ is hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;

R², R³, R⁴, and R⁶ are, independently, hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms

R⁵ is hydrogen or alkyl of 1 to 6 carbon atoms;

A dotted line represents an optional double bond;

A and D are selected from carbon, substituted by R¹, and nitrogen, provided that at least one of A and D is nitrogen;

E and G are carbon, substituted by R¹; and Z is N or CR⁶:

or pharmaceutically acceptable salts thereof, comprising the steps of:

a) halogenating a compound of the formula:

wherein R' is alkyl of 1-6 carbon atoms;

5 with a halogenating reagent to afford a compound of the formula:

wherein X is Br, Cl, or I;

b) dealkylating the compound of Formula 3 in an acid to afford a compound of the formula:

c) alkylating the compound of Formula 4 with R" protected glycidyl ethers (wherein R" is benzyl or substituted benzyl to afford compound of the formula:

d) cyclizing the compound of Formula 5 with palladium or copper catalyst to afford a
 compound of the formula:

e) debenzylating the compound of Formula 6 to afford the compound of the formula:

5

f) activating the hydroxy moiety of the compound of Formula 7 with with a sulfonating reagent to afford a compound of the formula:

10

wherein R" is an aryl- or alkyl- sulfonate; and

g) coupling the compound of Formula 8 with the appropriate azaheterocycle of Formula 9

15

in the presence of base to provide a compound of Formula I

$$R^3$$
 Z
 R^2
 $N-R^5$

5 2. A method of making compound of formula I:

$$R^3$$
 R^4
 R^2
 R^2
 $N-R^5$
 R^5

wherein

10

15

R¹ is hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;

R², R³, R⁴, and R⁶ are, independently, hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms

20 R⁵ is hydrogen or alkyl of 1 to 6 carbon atoms; A dotted line represents an optional double bond; A and D are selected from carbon substituted by R¹ and nitrogen, provided that at least one of A and D is nitrogen;

E and G are carbon, substituted by R^1 ; and

Z is N or CR⁶;

- 5 or pharmaceutically acceptable salts thereof, comprising the steps of
 - a) halogenating a compound of the formula:

wherein R' is alkyl of 1-6 carbon atoms;

with N-halosuccinimide in a solvent to afford a compound of the formula:

wherein X is Br, Cl, or I;

15

b) dealkylating the compound of Formula 3 in an acid to afford a compound of the formula:

c) alkylating the compound of Formula 4 with R" protected glycidyl ethers (OR') wherein R" is benzyl or substituted benzyl, or alkyl alcohol of 1 to 6 carbon atoms to afford compound of the formula:

d) cyclizing the compound of Formula **5** with palladium or copper catalyst to afford a compound of the formula:

5

e) debenzylating the compound of Formula 6 to afford the compound of the formula:

10

f) activating the hydroxy moiety of the compound of Formula 7 with alkyl- or arylsulfonyl chloride or with alkyl or aryl sulfonic anhydride in the presence of a base to afford a compound of the formula:

15

wherein R" is an alkyl- or aryl- sulfonate; and

g) coupling the compound of Formula 8 with the appropriate azaheterocycle of Formula 9

in the presence of base to provide a compound of Formula I.

5 3. A method of making compound of Formula la:

comprising the steps:

10 a) halogenating a compound of the formula:

wherein R' is alkyl of 1-6 carbon atoms;

with N-halosuccinimide in a solvent to afford a compound of the formula:

10

wherein X is Br, Cl, or I;

b) dealkylating the compound of Formula 3 in an acid to afford a compound of the formula:

c) alkylating the compound of Formula 4 with R" protected glycidyl ethers (wherein R" is benzyl or substituted benzyl;

to afford compound of the formula:

d) cyclizing the compound of Formula **5** with palladium or copper catalyst to afford a compound of the formula:

e) debenzylating the compound of Formula 6 to afford the compound of the formula:

20

f) activating the hydroxy moiety of the compound of Formula 7 with alkyl or aryl sulfonyl chloride with alkyl or aryl sulfonic anhydride in the presence of a base to afford a compound of the formula:

5

wherein R" is a alkyl- or aryl- sulfonate; and

g) coupling the compound of Formula 8 with 3-tetrahydropyridinyl-indole in the presence of base to provide a compound of Formula Ia.

10

- 4. The method of Claim 1 wherein the compound of Formula 2 is treated with N-halosuccinimide in acetonitrile.
- The method of Claim 1 wherein the halogenation reaction is quenched with a
 10% NaHSO3 solution and the product precipitated with NaOH.
 - 6. The method of Claim 1 wherein the compound of Formula 3 is dealkylated with a Lewis acid.
- 7. The method of Claim 1 wherein the compound of Formula 3 is dealkylated with a protic acid.
 - 8. The method of Claim 7 wherein the protic acid is HBr.
- 9. The method of Claim 8 wherein the compound of Formula 2 is heated to reflux in HBr for from about 6 to about 7 hours.
 - 10. The method of Claim 1 wherein the compound of Formula **4** is alkylated with benzyl- or substituted benzyl-glycidyl ether in a polar solvent.

11. The method of Claim 1 wherein the compound of Formula 4 is alkylated with benzyl glycidyl ether, 4-bromobenzyl glycidyl ether, 4-chlorobenzyl glycidyl ether, 3, 4-dimethoxybenzyl glycidyl ether, 2- or 4-nitrobenzyl glycidyl ether, or 4-methoxy-phenyl glycidyl ether.

5

- 12. The method of Claim 10 wherein the polar solvent is dimethylsulfoxide, dimethyl-formamide, or dimethylacetamide.
- 13. The method of Claim 10 wherein the base is triethylamine, sodium carbonate,10 or potassium carbonate.
 - 14. The method of Claim 1 wherein the compound of Formula 5 is cyclized using palladium catalyst in the presence of phosphine ligand and base.
- 15. The method of Claim 14 wherein the palladium catalyst is tris(dibenzylidene-acetone)dipalladium, tetrakis(triphenylphosphine)palladium, or palladium acetate with phosphine ligands selected from the group consisting of (±) 2,2'-bis(diphenyl-phosphino)-1,1'-binaphthyl and separate enantiomers thereof; (±) 2,2'-bis(di-p-tolyl-phosphino)-1,1'-binaphthyl and separate enantiomers thereof; 1-1'-bis(diphenyl-phosphino)ferrocene; 1,3-bis(diphenyl-phosphino)propane; and 1,2-bis(diphenyl-phosphino)ethane.
 - 16. The method of Claim 14 wherein the base is sodium hydride, lithium hydride, potassium hydride, potassium carbonate, sodium carbonate, titanium carbonate, cesium carbonate, potassium *t*-butoxide or potassium phosphate tribasic.
 - 17. The method of Claim 1 wherein the compound of Formula 5 is cyclized using copper catalyst in the presence of base.
- 30 18. The method of Claim 17 wherein the copper catalyst is copper iodide.
 - 19. The method of Claim 17 wherein the base is sodium hydride, lithium hydride or potassium hydride.

- 20. The method of Claim 1 wherein the compound of Formula **6** is debenzylated with Lewis acid, strong protic acid or under reductive cleavage conditions.
- 21. The method of Claim 20 wherein the Lewis acid is boron tribromide, boron trichloride, aluminum trichloride, ferric chloride or trimethylsilyl iodine.
 - 22. The method of Claim 20 wherein the protic acid is hydrobromic acid or hydrochloric acid.
- 10 23. The method of Claim 1 wherein a) the compound of Formula 5 is cyclized using copper catalyst in the presence of NaH to provide compound of Formula 6, and b) compound of Formula 6 is debenzylated with HCl to provide compound of Formula 7.
- 15 24. The method of Claim 20 wherein reductive cleavage is performed using palladium catalyst and hydrogen transfer reagents.
 - .25. The method of Claim 24 wherein the palladium catalyst is Pd/C.
- 20 26. The method of Claim 24 wherein the transfer reagent is cyclohexene, methylcyclohexene, ammonium formate or hydrogen.
 - 27. The method of Claim 24 wherein the palladium catalyst is Pd/C and the transfer reagent is cyclohexene.
 - 28. The method of Claim 1 wherein the compound of Formula 7 is activated with a sulfonating reagent or with an aryl or alkyl sulfonic anhydride in the presence of a base.
- 30 29. The method of Claim 28 wherein the compound of Formula **7** is activated with *p*-toluenesulfonyl chloride, methanesulfonyl chloride, 2-, 3- or 4-nitrobenzenesulfonyl chloride, 2- or 4-bromobenzenesulfonyl chloride or trifluoromethylsulfonic anhydride.

- 30. The method of Claim 28 wherein the compound of Formula 7 is activated with 4-bromobenzenesulfonylchloride.
- 31. The method of Claim 28 wherein the base is triethylamine or pyridine in methylene chloride, tetrahydrofuran, or toluene.
 - 32. The method of Claim 1 wherein the compound of Formula 8 is coupled with an azaheterocycle of Formula 9 in the presence of a base.
- 10 33. The method of Claim 32 wherein the base is sodium carbonate, potassium carbonate, or Hünig's base.
 - 34. A method of making compounds of Formula I:

15

20

wherein

- R¹ is hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;
- R², R³, R⁴, and R⁶ are, independently, hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms

R⁵ is hydrogen or alkyl of 1 to 6 carbon atoms;

A dotted line represents an optional double bond;

A and D are selected from carbon, substituted by R¹, and nitrogen, provided that at least one of A and D is nitrogen;

E and G are carbon, substituted by R¹; and

Z is N or CR⁶;

or pharmaceutically acceptable salts thereof, comprising the steps of:

a) halogenating a compound of the formula:

10

5

wherein R' is alkyl of 1-6 carbon atoms;

with N-halosuccinimide in a solvent to afford a compound of the formula:

15

wherein X is Br, Cl, or I;

b) dealkylating the compound of Formula 3 in an acid to afford a compound of the formula:

20

c) alkylating the compound of Formula **4** with R" protected glycidyl ethers (wherein R" is benzyl or substituted benzyl to afford compound of the formula:

25

d) cyclizing the compound of Formula 5 with palladium or copper catalyst to afford a compound of the formula:

5

e) debenzylating the compound of Formula 6 to afford the compound of the formula:

10

f) activating the hydroxy moiety of the compound of Formula 7 to a halide to afford a compound of the formula:

15 wherein X is I, Br or Cl and

g) coupling the compound of Formula **10** with the appropriate azaheterocycle of Formula **9**

$$R^3$$
 R^4
 R^2
 $N-R^5$

in the presence of base to provide a compound of Formula I.

- 5 35. The method of Claim 34 wherein the compound of Formula 7 is activated with a halogenating reagent.
- 36. The method of Claim 34 wherein the compound of Formula 7 is activated as a halide with phosphorous triiodide, phosphorous tribromide, phosphorous
 10 pentachloride or thionyl chloride.
 - 37. A method of making compounds of Formula I:

15 wherein

- R¹ is hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;
- R², R³, R⁴, and R⁶ are, independently, hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, trifluoromethyl, alkyl

of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms

R⁵ is hydrogen or alkyl of 1 to 6 carbon atoms;

A dotted line represents an optional double bond;

A and D are selected from carbon, substituted by R¹, and nitrogen, provided that at least one of A and D is nitrogen;

E and G are carbon, substituted by R¹; and

10 Z is N or CR^6 ;

or pharmaceutically acceptable salts thereof comprising the steps of:

a) halogenating a compound of the formula:

2

wherein R' is alkyl of 1-6 carbon atoms;

with N-halosuccinimide in a solvent to afford a compound of the formula:

20

15

5

wherein X is Br, Cl, or I;

b) dealkylating the compound of Formula 3 in an acid to afford a compound of the formula:

25

- 49 -

c) alkylating the compound of Formula 4 with R" protected glycidyl ethers (OR") wherein R" is benzyl or substituted benzyl to afford compound of the formula:

5d) cyclizing the compound of Formula 5 with palladium or copper catalyst to afford a compound of the formula:

e) debenzylating the compound of Formula 6 to afford the compound of the formula:

15 f) activating the hydroxy moiety of the compound of Formula **7** to a halide to afford a compound of the formula:

wherein X is I, Br or CI; and

5 g) coupling the compound of Formula **10** with the appropriate azaheterocycle of Formula **9**

$$R^3$$
 Z
 $N-R^5$

in the presence of base to provide a compound of Formula I.

10

38. A method of making a compound of Formula la:

comprising the steps:

a) halogenating a compound of the formula:

2a

wherein R' is alkyl of 1-6 carbon atoms;

with N-halosuccinimide in a solvent to afford a compound of the formula:

5 wherein X is Br, Cl, or I;

b) dealkylating the compound of Formula **3a** in an acid to afford a compound of the formula:

c) alkylating the compound of Formula **4a** with R" protected glycidyl ethers (wherein R" is benzyl or substituted benzyl; to afford compound of the formula:

d) cyclizing the compound of Formula **5a** with palladium or copper catalyst to afford a compound of the formula:

e) debenzylating the compound of Formula 6a to afford the compound of the formula:

f) activating the hydroxy moiety of the compound of Formula **7a** to a halide to afford a compound of the formula:

wherein X is I, Br or CI; and

- g) coupling the compound of Formula **10a** with 3-tetrahydropyridinyl-indole in the presence of base to provide a compound of Formula **Ia**.
 - 39. A method of preparing compounds of the formula 5:

15

20

wherein

R¹ is hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;

A and D are selected from carbon substituted by R¹ and nitrogen, provided that at least one of A and D is nitrogen;

E and G are carbon, substituted by R¹;

25 R" is benzyl or substituted benzyl;

and X is halogen; comprising alkylating the compound of formula **4**

- 5 with R" protected glycidyl ethers (OR").
 - 40. The method of Claim 39 wherein A is nitrogen, and D is carbon.
 - 41. A method of preparing a compound of Formula 6

10

15

R¹ is hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;

A and D are selected from carbon substituted by R¹ and nitrogen, provided that at least one of A and D is nitrogen;

E and G are carbon, substituted by R¹; and

20 R" is benzyl or substituted benzyl,

comprising the step of cyclizing a compound of Formula 5

with palladium or copper catalyst.

- 42. The method of Claim 41 wherein the catalyst is a palladium catalyst.
- 43. The method of Claim 41 wherein A is nitrogen and D is carbon.
- 44. A method of preparing a compound of Formula 10

wherein

5

- 10 R¹ is hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;
- 15 A and D are selected from carbon substituted by R¹ and nitrogen, provided that at least one of A and D is nitrogen;

E and G are carbon, substituted by R¹; and

X is I, Cl or Br:

comprising activating compound of Formula 7

20

to halide with a standard halogenating reagent.

45. The method of Claim 44 wherein the halogenating agent is halophosphorous.

10

15

- 46. The method of Claim 44 wherein the halophosphorous is phosphorous triiodide, phosphorous tribromide or phosphorous pentachloride.
- 47. The method of Claim 44 wherein A is nitrogen, and D is carbon.

48. A method of preparing a compound of Formula 8

wherein R¹ is hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;

A and D are selected from carbon substituted by R¹ and nitrogen, provided that at least one of A and D is nitrogen;

E and G are carbon, substituted by R¹; and

R" is an aryl- or alkyl- sulfonate;

comprising activating the hydroxy moiety of the compound of formula 7

20

with aryl or alkyl sulfonyl chloride or with aryl or alkyl sulfonic anhydride in the presence of a base.

49. The method of Claim 48 wherein A is nitrogen and D is carbon.

10

50. A method of preparing a compound of Formula 7

wherein R¹ is hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;

A and D are selected from carbon substituted by R¹ and nitrogen, provided that at least one of A and D is nitrogen; and

E and G are carbon, substituted by R1;

comprising debenzylating a compound of Formula 6

- where R" is benzyl or substituted benzyl.
 - 51. The method of Claim 50 wherein A is nitrogen, and D is carbon.
 - 52. A compound of the formula

wherein:

20

R¹ is hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms,

10

15

amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;

A and D are selected from carbon substituted by R¹ and nitrogen, provided that at least one of A and D is nitrogen;

E and G are carbon, substituted by R¹;

R₇ is hydroxy, alkoxy of 1-6 carbon atoms, or alkoxy of the formula

wherein R_9 is hydroxy, benzyl ether, substituted benzyl ethers such as 4-bromobenzyl ether, 4-chlorobenzyl ether, 3, 4-dimethoxybenzyl ether, 2- or 4-nitrobenzyl ether, or 4-methoxyphenyl; and

R₈ is halogen or hydrogen; and salts thereof.

- 53. A compound of Claim 52 wherein A is nitrogen and D is carbon.
- 54. A compound of the formula

wherein:

- 20 R¹ is hydrogen, hydroxy, halo, cyano, carboxamido, carboalkoxy of two to six carbon atoms, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;
- A and D are selected from carbon substituted by R¹ and nitrogen, provided that at least one of A and D is nitrogen;

E and G are carbon, substituted by R¹; and

R₁₀ is hydroxy, halide or alkyl- or aryl- sulfonates; and salts thereof.

30 55. A compound of Claim 54 wherein A is nitrogen and D is carbon.